

# **SPL Process ER/DL Meeting Meeting Minutes Apr 22, 2015**

**Chair of today's meeting:** Herb O'Brien

Today's meeting is a webex.

The normal Teleconference information:

USA Toll-Free 866-213-2145

USA Paid/International: 609-454-9913

Access code: 273 8216

Teleconference information: How to mute/unmute

#6: Mute

\*6: Unmute

Link to the SPL wiki:

<http://spl-work-group.wikispaces.com/share/view/51351516>

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Agenda:

## **1 PLLR Follow-up – Pregnancy section**

The new LOINC codes have been added to the list of SPL section headers:

<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162057.htm>.

## **2 Electronic Submission of Lot Distribution Reports**

### **Background**

- Final rule issued June 10, 2014
- Applicants required to submit LDRs to FDA in electronic format
- SPL is the standard for submission of LDRs
- Same message exchange recommended as used for establishment registration and drug listing
- CBER's LDR, FDA's ADR and Vaccine ADR databases linked to improve safety monitoring by product lot.

### **Lot Distribution Reports**

- To be submitted to CBER or CDER as appropriate
- LDRs submitted every 6 months
- Containing quantity of product distributed under BLA's (including to distributors)
- FDA may request more detailed information at any time
- Parameter values (Data Standards) should be drawn from FDA standards for SPL resources (link below)

- If additional values are needed request from SPL@fda.hhs.gov

#### Submitting Process

- LDRs submitted in eCTD Module3
- Title should be Lot-Distribution-Report-{Date of Submission}
- Lifecycle to follow current eCTD specifications
- A free tool for generating SPL files is available at
- <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm189651.htm>  
Step-by-step instructions for electronically creating, validating, and submitting self-identification information are available at
- <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>
- Software tools developed internally by generic manufacturers utilizing the SPL technical specifications.
- Transmit files as a BLA eCTD through the FDA's Electronic Submission Gateway (ESG)

#### Waiver Request

- Rarely FDA may grant a temporary waiver from the electronic submission process
- Consult FDA for technical help before submitting a waiver request

#### *Content of Waiver Requests*

- Explanation of why compliance no needed or possible (internet issues, acts of nature etc)
- Propose alternate submission format
- Mail request including all products covered in waiver
- Include an end date for waiver
- Alternative reporting methods can include physical media (paper, disk, fax etc)
- Heading **WAIVER REQUEST\_LOT DISTRIBUTION REQUIREMENTS** bold and capitalized

#### SUMMARY

The licensed manufacturer shall submit information about the quantity of the product distributed under the product license, including the quantity distributed to distributors. The interval between distribution reports shall be 6 months. Upon written notice, FDA may require that the licensed manufacturer submit distribution reports under this section at times other than every 6 months.

**Note:** In March and April 2015, CBER has been and will be conducting a lot distribution data SPL pilot. The outcome of that pilot could result in very minor adjustments to the lot distribution data SPL content in the aforementioned SPL implementation guide.

#### TERMS for LDRS

**Bulk Lot Number** - (from which the final container was filled)

**Fill Lot numbers** - for the total number of dosage units of each strength or potency distributed (e.g., fifty thousand per 10-milliliter vials)

**The Label Lot Number** - (if different from fill lot number), labeled date of expiration, number of doses in fill lot/label lot, date of release of fill lot/label lot for distribution at that time. If any significant amount of a fill lot/ label lot is returned, include this information.

#### 4. Jacqueline Bruner from i4i: Demonstrate Lot Distribution Reports using the i4i tool

##### Notepad rendition of data:

Sample lot distribution data includes 2 products, with 3 lots:

5643	654321	ANTIBIOTIX	1234-5555-01	B0001	F0001	L0001	257	6	1	06/24/2014	11/05/2016	07/01/2014	12/31/2014		D	I
5644	654322	ANTIBIOTIX	1234-5555-01	B0002	F0002	L0002	60	0	1	09/10/2014	12/01/2016	07/01/2014	12/31/2014		D	I
5645	654323	ANTIBIOTIX	1234-5555-01	B0003	F0003	L0003	398	0	1	04/23/2014	08/18/2015	07/01/2014	12/31/2014		D	I
5660	654338	ANTIBIOTIX	1234-6666-01	B0018	F0018	L0018	95	50	1	09-03/2014	12/28/2016	07/01/2014	12/31/2014		D	I
5661	654339	ANTIBIOTIX	1234-6666-01	B0019	F0019	L0019	10	0	1	09-03/2014	12/28/2016	07/01/2014	12/31/2014		I	I
5662	654340	ANTIBIOTIX	1234-6666-01	B0020	F0020	L0020	40	0	1	10-14/2014	01/25/2017	07/01/2014	12/31/2014		D	I

The data included column by column:

License Number | BLA | Product name | NDC | Bulk Lot Number | Fill Lot Number | Label Lot Number | Final # Containers Distributed | Final # Containers returned | # Doses per container | Initial Distribution Date | Labeled Expiry Date | Report Start Date | Report End Date | Package lot ID | Distribution Flag (foreign or domestic) | Distribution Type (per reporting interval or anticipated total)

There are a few more data fields that need to be included in the lot distribution report.

Following are screen shots that were captured during Jacqueline Bruner's demonstration. All images below are Copyright 2015 i4i.

##### Stylesheet: SPL rendition of same data:

ANTIBIOTIX

antibiotix solution

Product Information				
Product Type	VACCINE	Item Code (Source)	NDC:1234-6666	
Route of Administration	INTRAMUSCULAR	DEA Schedule		
Active Ingredient/Active Moiety				
Ingredient Name		Basis of Strength	Strength	
INFLUENZA A VIRUS A/CALIFORNIA/7/2009 (H1N1)-LIKE ANTIGEN (PROPIOLACTONE INACTIVATED) (UNII: CX39D2R810) (INFLUENZA A VIRUS A/CALIFORNIA/7/2009 (H1N1)-LIKE HEMAGGLUTININ ANTIGEN (PROPIOLACTONE INACTIVATED) - UNII:K9P8PVA2UG)		INFLUENZA A VIRUS A/CALIFORNIA/7/2009 (H1N1)-LIKE ANTIGEN (PROPIOLACTONE INACTIVATED)	12 ug in 1 mL	
HAEMOPHILUS INFLUENZAE (UNII: K738E2MB31) (HAEMOPHILUS INFLUENZAE - UNII:K738E2MB31)		HAEMOPHILUS INFLUENZAE	5 ug in 1 mL	
Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:1234-6666-02	1 in 1 CONTAINER		
1	NDC:1234-6666-01	10 mL in 1 VIAL; Type 0: Not a Combination Product		
Marketing Information				
Marketing Category		Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA		BLA654321	01/01/2015	

## Stylesheet - Labeler and manufacturing data.

**Labeler** - i4i Pharma (123456789)

### Establishment

Name	Address	ID/FEI	Business Operations
i4i Pharma		123456789	LABEL(1234-5555) , MANUFACTURE(1234-5555)

### Establishment

Name	Address	ID/FEI	Business Operations
i4i Labs		987654321	PACK(1234-6666) , MANUFACTURE(1234-6666, 1234-5555)

Revised: 4/2015

i4i Pharma

## Data in the i4i tool:

Edit Labeler and Manufacturing Information

LABELER, REGISTRANT, AND ESTABLISHMENT INFORMATION

Version:

Labeler Name:

i4i Pharma

DUNS Number:

123456789

Manufacturer License Number:

Contact Email:

Reporting Start Date:

Reporting End Date:

Establishments

Establishment 1

Company Name:

i4i Pharma

DUNS Number:

123456789

Confidential:

☐ Yes ☒ No

Establishment 2

Company Name:

i4i Labs

DUNS Number:

987654321

Confidential:

☐ Yes ☒ No

Print Preview

Validate

Save

Cancel

Edit Product Data Elements

**- BRAND NAME** Antibiotix **Product Code** 1234-6666 **APPLICATION NUMBER** BLA654321

**PRODUCT INFO**

**Dosage Form** SOLUTION

**Route Of Administration** INTRAMUSCULAR

**Dosing Specifics** Quantity:  Unit: MILLILITER ☐ Variable dose:

**Lot Data**

**- Fill Lot 1**

**Bulk Ingredient Information**

**INFLUENZA A VIRUS A/CALIFORNIA/7/2009 (H1N1)-LIKE ANTIGEN (PROPIOLACTONE INACTIVATED)**

Bulk Lot Number  Manufacturer I4I LABS DUNS 987654321

**HAEMOPHILUS INFLUENZAE**

Bulk Lot Number  Manufacturer I4I LABS DUNS 987654321

**Final Container Information**

**Final Container Details:** 10 mL In 1 VIAL (1234-6666-01)

Lot Number  Containers Distributed  Containers Returned

Expiry Date  Distribution Date  Distribution Type ☐ Distributed per reporting interval ☒ Anticipated total

**- MARKETING INFORMATION**

Category	Application Number or Monograph	Marketing Start Date	Marketing End Date

Print Preview Validate Save Cancel

Edit Product Data Elements

**Dosage Form** SOLUTION

**Route Of Administration** INTRAMUSCULAR

**Dosing Specifics** Quantity: 10 Unit: MILLILITER ☐ Variable dose:

**Lot Data**

**- Fill Lot 1** F0018

**Bulk Ingredient Information**

**INFLUENZA A VIRUS A/CALIFORNIA/7/2009 (H1N1)-LIKE ANTIGEN (PROPIOLACTONE INACTIVATED)**

Bulk Lot Number B0018 Manufacturer I4I LABS DUNS 987654321

**HAEMOPHILUS INFLUENZAE**

Bulk Lot Number B0018 Manufacturer I4I LABS DUNS 987654321

**Final Container Information**

**Final Container Details:** 10 mL In 1 VIAL (1234-6666-01)

Lot Number L0018 Containers Distributed 95 Containers Returned 50

Expiry Date 2014/07/30 Distribution Date 2012/02/14 Distribution Type ☒ Distributed per reporting interval ☐ Anticipated total

**+ Fill Lot 2** F0019

**+ Fill Lot 3** F0020

**+ MARKETING INFORMATION**

Category	Application Number or Monograph	Marketing Start Date	Marketing End Date

**- BRAND NAME** Antibiotix **Product Code** 1234-5555 **APPLICATION NUMBER** BLA123456

Print Preview Validate Save Cancel

## Variable lot distribution:

Edit Product Data Elements

- BRAND NAME Antibiotix		Product Code 1234-6666	APPLICATION NUMBER BLA654321
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PRODUCT INFO

Dosage Form

SOLUTION

Route Of Administration

INTRAMUSCULAR

Dosing Specifics

Quantity:

Unit:

Variable dose: ☒

Lot Data

+ Fill Lot 1

F0018

+ Fill Lot 2

F0019

+ Fill Lot 3

F0020

+ MARKETING INFORMATION

## SPL stylesheet version:

ANTIBIOTIX  
solution

Product Information									
Product Type		LOT DISTRIBUTION DATA			Item Code (Source)			NDC:1234-6666	
Active Ingredient/Active Moiety									
Ingredient Name					Basis of Strength			Strength	
INFLUENZA A VIRUS A/CALIFORNIA/7/2009 (H1N1)-LIKE ANTIGEN (PROPIOLACTONE INACTIVATED) (UNII: CX39D2R810) (INFLUENZA A VIRUS A/CALIFORNIA/7/2009 (H1N1)-LIKE HEMAGGLUTININ ANTIGEN (PROPIOLACTONE INACTIVATED) - UNII:K9P8PVA2UG)					INFLUENZA A VIRUS A/CALIFORNIA/7/2009 (H1N1)-LIKE ANTIGEN (PROPIOLACTONE INACTIVATED)			12 ug in 1 mL	
HAEMOPHILUS INFLUENZAE (UNII: K738E2MB31) (HAEMOPHILUS INFLUENZAE - UNII:K738E2MB31)					HAEMOPHILUS INFLUENZAE			5 ug in 1 mL	
Lot Distribution Data		Reporting Period		20150101-20150331		DUNS			
Fill Lot Number	Bulk Lot Number	Substance				Quantity	Unit	DUNS	
F0018	B0018	INFLUENZA A VIRUS A/CALIFORNIA/7/2009 (H1N1)-LIKE ANTIGEN (PROPIOLACTONE INACTIVATED)						987654321	
	B0018	HAEMOPHILUS INFLUENZAE						987654321	
Final Container Lot Number	NDC Package Code	Container Quantity (Doses)	Container Form	Distributed Containers (Doses)	Distribution Type	Initial Date	Expiration Date	Returned Containers (Doses)	DUNS
L0018	1234-6666-01	10 mL (1)	VIAL	95 (95)	Distributed per reporting interval	20120214	20140730	50 (50)	
Fill Lot Number	Bulk Lot Number	Substance				Quantity	Unit	DUNS	
F0019	B0019	INFLUENZA A VIRUS A/CALIFORNIA/7/2009 (H1N1)-LIKE ANTIGEN (PROPIOLACTONE INACTIVATED)						987654321	
	B0019	HAEMOPHILUS INFLUENZAE						987654321	

- **How often do you have to submit?** Minimum every 6 months, per regulations. However, some products may need to be submitted more often.
- **Tools:** Tools may handle the data differently. The i4i tool allows the import of the data from a text file. But other tools
- **Maintenance of the data:** New data needs to be input every 6 months, and the report created independently.
- **Validation to be done at the FDA?**
  - o Similar to what is done now
  - o Same set IDs for the same NDC.

## 5. Labeler Codes and transfer of ownership

**Question:** What is the impact in drug listings and transferring ownerships of labeler code – when, how, whom and how to mitigate impact in reimbursement.

- In similar situations, I have submitted a new SPL with a new set ID with our labeler code. I have left the previous SPL document (old set-id) posted for at least 6 months past the last lot expiration date and then would delist the product.
- If we purchased another company, I would follow the same procedure. The question is how would we be able to delist a SPL document that was done by the company we purchased?
  - If you have purchased a company and you acquire all of its assets, you should check with the proper legal person regarding the agreement and the person who handles reimbursements.
    - Ask for the previous documentation so you don't have to go to Lonnie.
  - **Lonnie:** For the NDC Labeler Code SPL file, you should request a previously submitted version and change the appropriate information in the SPL file.
- Drug product SPL files may be downloaded from DailyMed and updated with the delisting information by those now (after the acquisition/merger) authorized to update the information in those SPL documents.

EDRLS response: They prefer that the when a company is purchased that the labeling is revised with the labeler code of the purchasing company.

In the event that the new company wishes to maintain the labeler code of the acquired company, the labeler code registration would need to be obtained and updated. They suggest that this be done under a separate entity of the new company. In all cases, CMS needs to be contacted regarding reimbursement.



## 6. Proprietary and Generic names for authorized generics

Question: Kathleen Lins -How do you handle Proprietary and Non-proprietary names in the product data elements section of the SPL files?

Proprietary name: A name that a company uses for the commercial distribution of a drug product; may also be known as the brand name. Enter the brand name without trademark symbols in the BRAND NAME field. If the brand name has a descriptor, such as "extended release," enter it in the SUFFIX field.

Non-proprietary name: Enter the generic name (active ingredient) in the GENERIC NAME field.

- Kathy's product was sodium acetate, the generic name was listed as sodium acetate (anhydrous)
  - Even though sodium acetate anhydrous is the active ingredient, Lonnie stated it could not be the non-proprietary name and requested the change the non-proprietary name to show sodium acetate
  - The UNII for sodium acetate anhydrous was used and failed validation
  - I checked the chemical structure, no difference (except for water
  - $C_2H_3O_2.Na.3H_2O$  (sodium Acetate) contains water vs  $C_2H_3O_2.Na$  (sodium anhydrous) contains no water
- **Lonnie:** In the product data elements section, the non-proprietary name is based on the active ingredient but that does not mean that you should always use the preferred name of the UNII. The UNII preferred name is for the substance, not the product, sometimes following different naming conventions than those assigning the non-proprietary name so they are not always interchangeable.
- **Herb:** I always refer to my CMC group to check the active Ingredient, basis of strength, moiety etc. You should also refer to the UNIIIS, preferred substances list at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm189651.htm>
- **Ben's reply:** My recommendation based on the authorized generics that I have submitted would be that the brand name/proprietary name for the example below would be Methotrexate. This field seems to be based on how the packaging is done. The generic name / non-proprietary name should be Methotrexate Sodium. This should be the active ingredient as found on the FDA active ingredient-active moiety relationship/basis of strength list. Of course, every once and a while, they change things on this list.
- Check the FDA guidance on salt nomenclature in the non-proprietary names.

## **7. Transfer of Ownership of 510K**

Question: How to transfer ownership of a 510K on the FURLS website as many of our 510K's were acquired from other companies.

- <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/RegistrationandListing/default.htm>
- Transfer ownership of facility
- <http://www.fda.gov/Training/CDRHLearn/default.htm>

Follow the step by step instructions.

## **8. How do we capture that we are owners of the 510K but are sometimes using third parties to manufacture products?**

- CDRH Response: "The only option would be to add the activity Specification Developer to your device listing."
- Any questions contact: CDRH Registration and Listing <reglist@CDRH.FDA.GOV

## **9. When a bulk ingredient or API is imported into the US for further processing a bulk ingredient SPL must be done in order for the bulk ingredient/API shipment to be released.**

Foreign (shippers) drug listing codes are needed for clearance.

## **10. Are there any instances where it would be necessary to provide a bulk ingredient SPL for a finished product coming into customs?**

My response would be no, a finished product should already be drug listed. I would refer you to eDRLS@fda.hhs.gov

**11. Is there would be a need for the API source (establishment) to be identified with a bulk ingredient listing?**

The importer's information should be included in the establishment registration of the foreign drug site which is exporting the drug product to the US importer. The establishment's DUNS Number in the product SPL file is linked to the establishment's DUNS Number in the establishment registration SPL document which has the information about the importer as well.

From Lonnie- For both of those questions, the answer depends on whether if the API will be utilized in the manufacture of an animal drug or human drug. They should contact CVM or CDER, respectively, to inquire.

Some FDA inspectors at the port require that the API be drug listed also- if the API is manufactured outside the country.

1. API needs a separate drug listing.
2. Final product needs to be drug listed
3. Foreign manufacturer needs to be drug listed. (The need for this drug listing may depend on the port of entry. Atlanta requires this.)

API manufactured in the US and sent out of the US for manufacturing. Does the API require drug listing? All API sent out of the US should be drug listed. This is really important in case it ever would need to be returned to the US.